2012-1485
(Reexamination No. 95/000,443)

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

INSTITUT PASTEUR & UNIVERSITE PIERRE ET MARIE CURIE,

Appellant,

v.

DAVID J. KAPPOS, DIRECTOR,
UNITED STATES PATENT AND TRADEMARK OFFICE

Appellee,

and

PRECISION BIOSCIENCES, INC.,

Appellee.

Appeal from the United States Patent and Trademark Office, Board of Patent Appeals and Interferences.

(Caption continued on inside front cover)

BRIEF FOR APPELLEE PRECISION BIOSCIENCES, INC.

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April 18, 2013

2012-1486
(Reexamination No. 95/000,490)

INSTITUT PASTEUR & UNIVERSITE PIERRE ET MARIE CURIE,

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CERTIFICATE OF INTEREST

Counsel for the Appellee Precision BioSciences, Inc. certifies the following:

1. The full name of every party or amicus represented by me is:

Precision BioSciences, Inc.

2. The name of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

Not applicable.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

Not applicable.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

WILMER CUTLER PICKERING HALE AND DORR LLP: Michael J. Twomey, Andrej Barbic.

/s/ Michael J. Twomey
MICHAEL J. TWOMEY

Dated: April 18, 2013

TABLE OF CONTENTS

TABLE OF AUTHORITIES

CASES

Page(s)

STATEMENT OF RELATED CASES

Two of the reexamined patents, U.S. Patent No. 6,610,545 and U.S. Patent No. 7,309,605, have been asserted by Cellectis SA, Pasteur's licensee, against Precision BioSciences, Inc., one of the Appellees, in Cellectis SA v. Precision BioSciences, Inc., No. 5:08-cv-119 (E.D.N.C.).

STATEMENT OF JURISDICTION

On March 15, 2012, the Board of Patent Appeals and Interferences ("Board") of the United States Patent and Trademark Office ("PTO") issued decisions in *Inter Partes* Reexamination Nos. 95/000,443; 95/000,490; and 95/000,491. Institut Pasteur ("Pasteur") timely appealed. This Court has jurisdiction under 28 U.S.C. §1295(a)(4)(A).

STATEMENT OF ISSUES

Appeal No. 2012-1487:

1. Whether the Board erred in finding that substantial evidence supports the Examiner's and Board's conclusion that the prior art provided motivation to perform the methods of claims 10 and 12 of U.S. Patent 6,610,545 with a reasonable expectation of success.

2. Whether the Board properly gave the claims their broadest reasonable interpretation, including the limitation of a "viable" cell.

Appeal No. 2012-1486:

1. Whether the Board erred in finding that substantial evidence supported the Examiner's and Board's conclusion that the prior art provided motivation to perform the method of claim 14 of U.S. Patent No. 7,309,605 with a reasonable expectation of success.

2. Whether the appeal of claim 14 is moot and should be dismissed because claim 14 was substantively amended during the reexamination and U.S. Patent No. 7,309,605 has now expired.

Appeal No. 2012-1485:

1. Whether the Board erred in finding that substantial evidence supported the Examiner's and Board's conclusion that the prior art provided

motivation to make the products claimed in U.S. Patent No. 6,833,252 with a reasonable expectation of success.

2. Whether the Board properly gave the claims their broadest reasonable interpretation, including the limitation of an "exogenous Group I intron encoded endonuclease site."

STATEMENT OF THE CASE

A. Preliminary Statement

The three patents at issue in this appeal (the "Appealed Patents") are part of a family of thirteen patents by inventors Dujon *et al.* (the "Dujon Patents"). The subject matter of the Dujon Patents relates to an enzyme from yeast named *I-SceI* (usually pronounced "eye-skee-one" by those of skill in the art), and each of the Dujon Patents is entitled "Nucleotide Sequence Encoding the Enzyme *I-SceI* and the Uses Thereof." That title accurately captures the inventive contribution disclosed in the Dujon Patents.

I-SceI is one of a group of naturally-occurring enzymes called "Group I intron-encoded endonucleases" (GIIEEs) that can cleave double-stranded DNA molecules only at positions that have specific sequences of the four nucleotides of DNA (*i.e.*, A, T, C and G) called "recognition sequences."

For many years before the applications leading to the Dujon Patents were filed, both GIIEEs and the effects of double-strand breaks in DNA had been studied and characterized. For example, *I-SceI* was first described by Jacquier and Dujon (1985) ('545 Patent, col. 2, ll. 33-37; '605 Patent, col. 2, ll. 41-45; '252 Patent, col. 2, ll. 33-37), and another GIIEE, named *I-TevI* (usually pronounced "eye-teev-one" by those of skill in the art), was first described by Chu *et al.* (1990) ('545 Patent, col. 10, ll. 20-21; '605 Patent, col. 12, ll. 62-63; '252 Patent, col. 12,

ll. 51-52). Moreover, the relationship between double-strand breaks in DNA and genetic recombination was well known, as described in detail in the Dujon Patents:

> One of the key issues in understanding genetic recombination is the nature of the initiation step. Studies of homologous recombination in bacteria and fungi have led to the proposal of two types of initiation mechanisms ... [In the second model], a double-strand break may occur, followed by a repair mechanism that uses an uncleaved homologous sequence as a template. This latter model has gained support from the fact that integrative transformation in yeast is dramatically increased when the transforming plasmid is linearized in the region of chromosomal homology and from the direct observation of a double-strand break during mating type interconversion of yeast. Recently, double-strand breaks have also been characterized during normal yeast meiotic recombination.

('545 Patent, col. 1, l. 60 – col. 2, l. 12; '605 Patent, col. 2, ll. 1-20; '252 Patent, col. 1, l. 60 – col. 2, l. 12; citations omitted).

The Dujon Patents did not add significantly to the general knowledge in the art relating to GIIEEs and their potential uses in promoting genetic recombination. They did, however, disclose for the first time a "universal code equivalent" nucleotide sequence encoding *I-SceI*, which allowed researchers for the first time to produce the *I-SceI* enzyme in eukaryotic cells (*i.e.*, cells with nuclei, ranging from yeast to humans).

Interestingly, in each of the first <u>*seven*</u> of the Dujon Patents, all filed before the Patent Owner licensed the Dujon Patent family to a company named Cellectis, SA in the year 2000, each and every independent claim was specifically limited to *I-SceI*. (See issued claims of U.S. Pat. No. 5,474,896, U.S. Pat. No. 5,792,632,

U.S. Pat. No. 5,866,361, U.S. Pat. No. 5,948,678, U.S. Pat. No. 5,962,327, U.S. Pat. No. 6,238,924 and U.S. Pat. No. 6,395,959). After the Dujon Patent family was licensed to Cellectis, in *five of the last six* Dujon Patents, including the three Appealed Patents, each and every independent claim was broadened to recite not only *I-SceI*, but either the *entire genus* of GIIEEs or a Markush group including at least *eleven GIIEEs* discovered and characterized by other researchers. (See issued claims of U.S. Pat. No. 6,610,545, U.S. Pat. No. 6,822,137, U.S. Pat. No. 6,833,252, U.S. Pat. No. 7,214,536 and U.S. Pat. No. 7,309,605).

The invalidity of the Appealed Patents stems directly from this broadening of the scope of the patents beyond the inventive contribution of a "Nucleotide Sequence Encoding the Enzyme *I-SceI* and the Uses Thereof." In particular, it stems from the attempts of the patentee to claim uses not only of I-SceI, but of *all* GIIEEs to practice methods which were anticipated or rendered obvious by the prior art, including the *Quirk*, *Bell-Pedersen* and *Eddy92* references discussed below, before the first of the Dujon Patents were filed.

B. Course of Proceedings and Disposition Below

Precision submits that Pasteur's summary of the course of proceedings and disposition below is substantially correct except that, in its Preliminary Statement, (a) Pasteur omits the fact that, despite having requested an oral hearing before the Board, the attorneys of record for Pasteur then waived their opportunity to appear

before the Board, (b) Pasteur has the temerity to complain that "Pasteur had no opportunity to present evidence" at a hearing it failed to attend and (c) and Pasteur now insults the Board, gratuitously and without justification, for "nonsensical supposition," "strained reasoning," and "hindsight divorced from the real world."

STATEMENT OF FACTS

A. Background and Prior Art

1. Technical Background

Precision submits that Pasteur's summary of the "Technical Background" is substantially correct except that:

Pasteur suggests that the Appealed Patents "involve a special class of endonucleases discovered by the Pasteur inventors in the mid-1980s." (Appellant's Brief 8). Each of the Appealed Patents includes a table that lists a variety of Group I intron encoded endonucleases (GIIEEs) and provides a reference to a scientific paper describing each. ('545 Patent, col. 10. ll. 8-30; '605 Patent, col. 12, l. 50 – col. 13, l. 10; '252 Patent, col. 12, ll. 40-60). These references make clear that, although the discovery of the first GIIEE, I-SceI, was the work of Dujon *et al.* at Pasteur, other groups were responsible for the discovery of other GIIEEs. For example, the I-SceII endonuclease was discovered at the Ecole Normale Superieure by Delahodde *et al.* (1989), and the I-CeuI endonuclease was discovered at the Universite Laval, Quebec by Lemieux and Lee (1987).

2. The Problem Addressed by the Pasteur Patents

The problem addressed by the Appealed Patents is accurately reflected in the title of each patent: "Nucleotide Sequence Encoding the Enzyme *I-SceI* and the Uses Thereof."

That is, the problem addressed is the provision of a "universal code equivalent" nucleotide sequence encoding the *I-SceI* endonuclease. This was a non-trivial task because the *I-SceI* endonuclease is encoded in the mitochondrial DNA of a yeast, and because that yeast mitochondrial DNA employs a genetic code that is slightly different from the "universal code" that is generally employed in nature.

This contribution was expressed not only in the title of the Dujon Patents, but was explicitly stated in the Abstract of each of the Dujon Patents:

> An isolated DNA encoding the enzyme I-SceI is provided. The DNA sequence can be incorporated in cloning and expression vectors, transformed cell lines and transgenic animals. The vectors are useful in gene mapping and site directed insertion of genes.

('545 Patent, Abstract; '605 Patent, Abstract; '252 Patent, Abstract)

This contribution was also made explicit in the Summary of the Invention of each of the Dujon Patents, where every aspect of the invention is described as limited to the nucleotide sequence encoding *I-SceI* or the *I-SceI* enzyme itself:

> SUMMARY OF THE INVENTION
>
> Accordingly, this invention aids in fulfilling these needs in the art. Specifically, this invention relates to an isolated DNA encoding the enzyme I-SceI. The DNA has the following nucleotide sequence:
>
> [SEQUENCE OMITTED]

> This invention also relates to a DNA sequence comprising a promoter operatively linked to the DNA sequence of the invention encoding the enzyme I-SceI.
>
> This invention further relates to an isolated RNA complementary to the DNA sequence of the invention encoding the enzyme I-SceI and to the other DNA sequences described herein.
>
> In another embodiment of the invention, a vector is provided. The vector comprises a plasmid, bacteriophage, or cosmid vector containing the DNA sequence of the invention encoding the enzyme I-SceI.
>
> In addition, this invention relates to *E. coli* or eukaryotic cells transformed with a vector of the invention.
>
> Also, this invention relates to transgenic animals containing the DNA sequence encoding the enzyme I-SceI and cell lines cultured from cells of the transgenic animals.
>
> In addition, this invention relates to a transgenic organism in which at least one restriction site for the enzyme I-SceI has been inserted in a chromosome of the organism.
>
> Further, this invention relates to a method of genetically mapping a eukaryotic genome using the enzyme I-SceI.
>
> This invention also relates to a method for in vivo site directed recombination in an organism using the enzyme I-SceI.

Thus, the problem solved by the Dujon Patents was clearly envisaged by the inventors themselves as the provision of a nucleotide sequence encoding *I-SceI* such that various *prior art methods and products* could be practiced with the *I-SceI* endonuclease rather than other known homing endonucleases.

B. The Pasteur Patents

Three of the Dujon patents are at issue in this appeal.

1. U.S. Patent 6,610,545

The '545 Patent issued on August 26, 2003, with 27 claims. Claims 7-27 were reexamined. A121. Pasteur is appealing the rejection of claims 10 and 12.

Claims 10 and 12 are dependent upon claim 7, which reads as follows (with underlining indicating a reexamination amendment):

> A method for in vivo site directed genetic recombination in an organism comprising:
>
> (a) providing a transgenic <u>eukaryotic</u> cell having at least one Group I intron encoded endonuclease recognition site inserted at a unique location in a chromosome;
>
> (b) providing an expression vector that expresses said endonuclease in said transgenic cell;
>
> (c) providing a plasmid comprising a gene of interest and a DNA sequence homologous to the sequence of the chromosome, allowing homologous recombination;
>
> (d) transfecting said transgenic cell with said plasmid of step (c);
>
> (e) expressing said endonuclease from said expression vector in said cell; and
>
> (f) cleaving said at least one Group I intron encoded endonuclease site with said endonuclease, whereby said cleavage promotes the insertion of said gene of interest into said chromosome of said organism at a specific site by homologous recombination.

Thus, a eukaryotic cell is genetically modified by inserting a GIIE endonuclease recognition site into a unique location in a chromosome of the cell. The cell is then further modified by inserting an expression vector that enables the cell to make the GIIE endonuclease and a plasmid containing a gene of interest and a DNA sequence homologous to the sequence of the chromosome. When the cell expresses the endonuclease, the endonuclease cleaves the chromosome at the recognition site, and the gene of interest integrates into the chromosome.

Dependent claims 10 and 12 limit the "organism" to "yeast" and "a mammal."

Because independent claim 7 has been amended, claims 10 and 12 which depend therefrom have also been amended.

2. U.S. Patent 7,309,605

The '605 Patent issued on December 18, 2007, with 17 claims. All 17 claims were reexamined. A77. Pasteur is appealing the rejection of claim 14.

Claim 14 is dependent upon claim 1. Claim 1 reads as follows (with underlining indicating reexamination amendments):

> A method for inducing at least one site directed double-stranded break in the chromosomal DNA of an organism comprising:
>
> (a) providing an isolated, viable cell of said organism containing at least one Group I intron encoded endonuclease site at a location in the chromosomal DNA of the cell,
>
> (b) providing said Group I intron encoded endonuclease to said cell by genetically modifying the cell with a nucleic acid comprising said Group I intron encoded endonuclease or by introducing said Group I intron encoded endonuclease protein into the cell such that the Group I intron encoded endonuclease cleaves said Group I intron encoded endonuclease site at the location in the chromosomal DNA of the cell.

Claim 14 reads as follows (again with underlining indicating a reexamination amendment):

> The method of claim 1, wherein said method further comprises providing to said cell

> a plasmid comprising a DNA sequence homologous to the sequence of the chromosome, which allows homologous recombination, and
>
> a modified sequence,
>
> wherein said Group I intron encoded endonuclease cleaves the Group I intron encoded endonuclease recognition site,
>
> whereby said cleavage promotes the insertion of said modified sequence into said chromosomal DNA of said cell at a specific site by homologous recombination.

3. U.S. Patent 6,833,252

The '252 patent issued on December 21, 2004, with 19 claims. All 19 claims were reexamined. A62. Claim 19's patentability was confirmed, and Pasteur is appealing the rejection of claims 1-18.

Claim 1 is the only independent claim and reads as follows:

> A recombinant mammalian chromosome comprising an exogenous Group I intron encoded endonuclease site,
>
> wherein the endonuclease site is within an integrated nucleic acid sequence from a vector,
>
> wherein the site is selected from the group consisting of an I-SecIV site, an I-CsmI site, [an] I-PanI site, [an] I-SceII site, an I-CeuI site, an I-PpoI site, an I-SceIII site, an I-CreI site, an I-TevI site, an I-TevII site, an I-TevIII site, and an I-SceI site.

SUMMARY OF THE ARGUMENT

Appeal No. 2012-1487: U.S. Patent 6,610,545. The Board's finding that claims 10 and 12 of Pasteur's '545 Patent would have been obvious was supported by substantial evidence and should be affirmed. In particular, the Board was

correct in finding that *Quirk* or *Bell-Pedersen* provided motivation to use GIIEEs to cleave chromosomes and insert exogenous genes, and *Eddy92* clearly suggested the method and explicitly referenced Bell-Pedersen as the model. Pasteur's argument that "all three references took steps to prevent chromosomal cleavage" is a red herring intended to obscure the teachings regarding *desired* chromosomal cleavage by reference to steps taken to minimize *undesired* chromosomal cleavage. Furthermore, the Board correctly found that *Frey* and *Dujon90* provided a reasonable expectation of success, because *Frey* and *Dujon90* used GIIEEs to cleave chromosomes, showing that they were effective with chromosomal DNA. Finally, the Board correctly discounted Pasteur's "objective evidence of nonobviousness" because it failed to establish a nexus with the claimed invention.

Appeal No. 2012-1486: U.S. Patent 7,309,605. The Board's finding that claim 14 of Pasteur's '605 Patent would have been obvious was supported by substantial evidence. The Board correctly found that *Eddy92* and either *Quirk* or *Bell-Pedersen* provided motivation to use GIIEEs to cleave chromosomes and insert exogenous genes, and the Board again correctly found that *Frey* and/or *Dujon90* provided a reasonable expectation of success. Moreover, Pasteur's appeal of claim 14 became moot when the '605 Patent expired, as the PTO has argued, because its scope was substantially changed by amendments during reexamination. Finally, the Board considered Pasteur's "objective evidence of

nonobviousness" which was submitted for all three of the Appealed Patents and correctly found that it failed to establish a nexus with the claimed invention.

Appeal No. 2012-1485: U.S. Patent 6,833,252. The Board's finding that the claims of Pasteur's '252 patent would have been obvious is supported by substantial evidence. The Board correctly found that *Old* or *Eddy92* in combination with *Quirk* or *Bell-Pedersen* provided motivation to make the claimed invention. The Board also correctly construed the term "endonuclease site" to require only a DNA sequence and not "endonuclease activity," and found that there was a reasonable expectation of success in practicing the claimed invention. Finally, the Board considered Pasteur's "objective evidence of nonobviousness" which was submitted for all three of the Appealed Patents and correctly found that it failed to establish a nexus with the claimed invention.

ARGUMENT

I. THE OBVIOUSNESS REJECTION FOR CLAIMS 10 AND 12 OF THE '545 PATENT SHOULD BE AFFIRMED

Claims 10 and 12 of the '545 Patent cover methods for inserting a gene of interest into a specific site in the chromosomal DNA of a yeast or mammal by using a GIIEEs to promote homologous recombination. A452(49:59-67, 50:58-67); A453(51:40-41, 52:3-4). The Board found that these claims would have been obvious because (1) one skilled in the art would have been motivated to combine *Eddy92* with *Quirk* or *Bell-Pedersen* to perform the claimed invention, and (2)

Frey and *Dujon90* would have provided a reasonable expectation of success. A128; A131. Both findings were supported by substantial evidence.

A. Pasteur Should Not Be Permitted to Raise New Arguments on Appeal

"The Board is an expert body that plays an important role in reviewing the rejection of patent applications. In a proceeding before the Board the applicant is given full 'opportunity to bring forth the facts thought necessary to support his or her position.'" *In re Watts*, 354 F.3d 1362, 1367 (Fed. Cir. 2004) (quoting *In re Gartside*, 203 F.3d 1305, 1314 (Fed. Cir. 2000). The Federal Circuit's "review of the Board's decision is confined to the 'four corners' of [the] record." *Id.* Therefore, "it is important that the applicant challenging a decision not be permitted to raise arguments on appeal that were not presented to the Board." *Id.*

Failure of an appellant to raise an issue before the Board therefore waives the argument on appeal absent special circumstances. *See In re Suitco Surface, Inc.*, 603 F.3d 1255, 1261 (Fed. Cir. 2010) ("Without any reason for its decision not to separately argue claim 6 before the Board, Suitco has waived its separate anticipation argument on appeal."); *In re Watts*, 354 F.3d at 1368 ("Because the appellant failed to argue his current interpretation of the prior art below, we do not have the benefit of the Board's informed judgment on this issue for our review. Moreover, Watts has shown no reason why we should excuse his failure to raise this argument before the Board."). The Federal Circuit's rule with respect to

arguments waived before the Board "is the same rule we follow in appeals from district courts and other agencies." *In re Watts*, 354 F.3d at 1368.

"While appellate courts are given the discretion to decide when to deviate from this general rule of waiver, we have explained that 'prudential considerations' articulated by the Supreme Court counsel against hearing new arguments for the first time on appeal absent limited circumstances …" *Golden Bridge Tech., Inc. v. Nokia, Inc.*, 527 F.3d 1318, 1322-1323 (Fed. Cir. 2008) (citing *Singleton v. Wulff*, 428 U.S. 106, 121 (1976)).

"[T]o prevent a party from clarifying or defending the *original scope* of its claim construction, or from supporting its *existing claim construction* position with new citations to the specification,' we have often barred parties from changing the scope of their claim construction position on appeal." *In re Watts*, 354 F.3d at 1368 n.3 (quoting *Interactive Gift Express, Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1346 (Fed. Cir. 2001)).

1. Pasteur's Argument that *Bell-Pedersen*, *Quirk*, and *Eddy92* Teach Away from the Claimed Invention Is a New Argument Raised on Appeal

Pasteur argues that *Bell-Pedersen*, *Quirk* and *Eddy92* teach away from the claimed invention because, allegedly, "each took affirmative steps to prevent cleavage of the host cell chromosomes." Appellant's Br. 37-39.

These arguments, however, are nowhere to be found in Pasteur's Appeal Brief submitted to the Board. Patent Owner's Br. A7564-7643. Moreover, as no representative of Pasteur appeared before the Board at oral argument, Pasteur waived that opportunity to make these arguments before the Board.

2. Pasteur's Argument that the Board Misinterpreted *Dujon90* Is a New Argument Raised on Appeal

Pasteur argues that the Board misinterpreted the teachings of *Dujon90* and wrongly concluded that *Dujon90* teaches that it would be predictable that a GIIEE could cleave a chromosome. Appellant's Br. 41-43.

This argument, however, is nowhere to be found in Pasteur's Appeal Brief submitted to the Board. Moreover, as no representative of Pasteur appeared before the Board at oral argument, Pasteur waived that opportunity to make this argument before the Board. Indeed, Pasteur did not even mention the *Dujon90* reference at all in the Appeal Brief it submitted to the Board.

3. Pasteur's Argument that the Board Misconstrued the Limitation "Viable" Is a New Argument Raised on Appeal

Pasteur argues that "viability is an *inherent* requirement in the claims" (emphasis added), that the Board wrongly concluded that the claims "do not expressly require that cells *remain* viable" (emphasis added), and therefore the Board discounted the teachings regarding toxicity in the prior art. Appellant's Br. 43-44.

This argument, however, is nowhere to be found in Pasteur's Appeal Brief submitted to the Board. Moreover, as no representative of Pasteur appeared before the Board at oral argument, Pasteur waived that opportunity to make this argument before the Board. Indeed, aside from a statement that "the invention's intended use required a viable cell" (Patent Owner's Br. 39, A7606), Pasteur did not discuss the term "viable" at all in the Appeal Brief it submitted to the Board.

B. The Board Correctly Found that the Subject Matter of Claims 10 and 12 Was Obvious Over *Quirk* and *Bell-Pedersen* in View of *Eddy92*

1. *Bell-Pedersen*, *Quirk*, and *Eddy92* Did Not Teach Away from Pasteur's Invention

As noted above, Pasteur's argument that *Bell-Pedersen*, *Quirk* and *Eddy92* teach away from the claimed inventions because "each took affirmative steps to prevent cleavage of the host cell chromosomes" (Appellant's Br. 37) is a new argument raised on appeal and should not be entertained.

In any event, however, the argument is not only without merit, but is inconsistent with Pasteur's other arguments. On the one hand, Pasteur argues that it was not obvious that GIIEEs could cleave chromosomal DNA, and on the other hand Pasteur argues that the authors of the *Quirk* and *Bell-Pedersen* were actively taking steps to prevent the GIIEs from cleaving chromosomal DNA. Why would those scientists have taken steps to reduce (not "prevent," as argued below)

chromosomal cleavage unless it was obvious that chromosomal cleavage otherwise would occur?

As explained by Dr. Deborah Bell-Pedersen in her declaration submitted December 16, 2009 in the '545 Reexam:

> 9. The Quirk *et al.* (1989) paper discloses the fact that expression of I-TevI and I-TevII [*i.e.*, two GIIEs] in *E. coli* can be toxic. For example, Quirk *et al.* (1989) states (paragraph bridging pgs 456-457):
>
> > However, during the course of our experiments, we noted that transformants containing [GIIE] clones with intact [gene] sequences grew poorly compared with transformants containing clones in which the [genes] were disrupted. This apparent toxicity of the [gene] product was pronounced when the [GIIEE] gene was cloned in a high copy number plasmid under p*lac* control, resulting in variable recombination frequencies.
>
> * * *
>
> 11. The passage describes the observation that expression of [GIIEs] in *E. coli* cells had a toxic effect, manifested by poor growth. When the [genes] were present in high copy number plasmids under control of the p*lac* promoter, [either GIIE] was expressed at relatively higher levels, and the toxicity was pronounced.
>
> 12. At the time of publication, I believed that the toxicity was the result of cleavage of the *E. coli* chromosome at one or more naturally-occurring recognition sites for [the GIIEs] because, if such sites were cleaved and not repaired, or were cleaved at a rate faster than the natural *E. coli* repair mechanisms could repair them, toxicity would be expected. Although other explanations were possible, I considered these less likely.
>
> 13. I believe that, at the time of publication of the Quirk *et al.* (1989) reference, the intended audience for the Quirk *et al.* (1989) reference would have understood that the toxicity was probably the

result of cleavage of the *E. coli* chromosome at one or more naturally-occurring recognition sites for [the GIIEEs].

14. The Quirk *et al.* (1989) paper discusses the efforts of myself and my co-authors to reduce the toxicity of [GIIEE] expression in *E. coli* (pg. 457, first paragraph):

> Therefore, further experiments were performed with [GIIE gene] fragments cloned in the lower copy number plasmid pKC30, under control of the more tightly regulated phage λ p_L promoter. Two different lambda lysogens were used: RRI(λc+), in which p_L is highly repressed by the wild-type lambda repressor, and N99(λ*bio*10*c*1857*P*am3) [referred to as N99(λ*c*1857) throughout this paper], in which p_L is controlled by the temperature-sensitive *c*I857 repressor, which allows low level expression at permissive temperatures (30°C-32°C) and high level expression at elevated temperatures (37°C-43°C).

15. In this passage, my co-authors and I describe the use of a low copy number plasmid (pKC30), which results in relatively lower [GIIEE] expression, and two different host cells (*E. coli* lysogens) with different "repressors" to control [GIIEE] expression. One host cell (RRI(λc+)), resulted in very low expression of [GIIE], but did not eliminate [GIIEE] expression. The other host cell (N99(λ*c*1857)), resulted in low level expression of [GIIEE] at 30°C, but high level expression at 37°C.

16. The expression of [GIIEE] from the low copy number pKC30 plasmid in the RRI(λc+) lysogen or the N99(λ*c*I857) lysogen at 30°C did not result in poor growth of the *E. coli* lysogens. This suggests that the lower levels of [GIIEE] were not toxic (or less toxic) because they resulted in cleavage of the naturally-occurring [GIIEE] recognition sites at rates sufficiently low to allow for successful repair by the natural *E. coli* repair mechanisms.

A13298-13300 (footnotes omitted).

The issue of GIIEE-mediated toxicity in the *Quirk* and *Bell-Pedersen* references is discussed at length in the Right of Appeal Notice issued in the '545 Reexam. In pertinent part, the examiner concluded:

> [C]ommon sense dictates that one would expect 'cellular toxicity' to be a likely effect of any enzyme which cleaves chromosomal DNA in a cell, such as the group I intron encoded endonucleases, or example; however, the solution to the toxicity issue is clearly set forth in each of Bell-Pedersen and Quirk, the two primary references which have been used in all of the obviousness rejections herein.
>
> Dr. Bell-Pedersen, who is the lead author of the Bell-Pedersen reference and co-author of the Quirk reference, speaks directly to the toxicity issue in the Second Bell-Pedersen Declaration, stating that such toxicity is likely a result of introduction of more double stranded break events in the host cell chromosome than can be repaired (see in particular, ¶¶ 13-14). Dr. Bell-Pedersen reports resolving the toxicity issue by selecting appropriate plasmid vectors to reduce the number of double-stranded break events, thus allowing for successful repair by the natural host cell mechanisms (see in particular, ¶¶ 18-23) ….
>
> The prior art, taken as a whole, and especially the primary references used in the rejections herein, do not teach away from using group I intron encoded endonucleases to introduce a double stranded break into a target nucleic acid sequence in the chromosomal DNA of a cell because they were know[n] to cause cellular toxicity; rather, as is demonstrated by the aforementioned teachings set forth in Quirk and Bell-Pedersen, the prior art of record taken as a whole points directly to the use of group I intron encoded endonucleases for efficient transfer of a gene of interest to a host cell and instructs one of ordinary skill in the art at the time of the invention how to use the endonucleases to accomplish this without associated cellular toxicity.

A6594-6596.

The issue with *Eddy92* is the same (although, here, it appears that the issue was not raised even before the examiner in reexamination). The Abstract of *Eddy92* states:

> There exist several examples of mobile group I introns. These introns appear to use a straightforward mechanism to achieve highly site-specific and efficient insertion into homologous intronless genes. Because the only intron-specific function required by the prevailing model for the mechanism of intron mobility the introduction of a site specific double-stranded break in the intronless recipient DNA molecule, we reasoned that it should in principle be possible to construct artificially mobile DNA sequences. We have constructed an artificial mobile element from the gene for the restriction enzyme EcoRI that is capable of site-specific insertion at rates near those of authentic mobile introns. The generality of the mobility mechanism may enable high efficiency targeted gene replacements or disruptions in a variety of organisms.

A9256.

Thus, *Eddy92* essentially replaced the GIIEE of *Quirk* and *Bell-Pedersen* with the endonuclease "EcoRI."

Like, *Quirk* and *Bell-Pedersen*, *Eddy92* sought to reduce chromosomal cleavage while allowing cleavage of the desired target in the chromosome. Thus, *Eddy92* used an enzyme that "methylates" the EcoRI target sites to prevent *undesired* chromosome cleavage but used an "unmethylated" target to allow the *desired* chromosome cleavage:

> The recipient DNA in these experiments is the genome of the bacteriophage λgt11, which contains a single EcoRI recognition site in the C terminus of the β-galactosidase gene lacZ (Fig. 2) (11). Using a phage genome as the recipient allowed us to mimic the extreme site

> specificity of natural intron-encoded homing endonucleases; expression of the EcoRI methylase from the mobile element (see below) modifies genomic EcoRI sites and makes the incoming λgt11 EcoRI site functionally unique.

A9258.

Therefore, even if Pasteur had argued this issue before the Board, there was clearly substantial evidence for the Board to conclude that there was no "teaching away" in *Quirk*, *Bell-Pedersen* or *Eddy92*.

2. *Eddy92*'s Statements About GIIEEs Were Not Mere Speculation

Eddy92 concludes with the following suggestion:

> It should be possible to use DSBR-based targeting of homologous recombination to effect site-directed gene conversions in a variety of organisms. The extreme specificity of intron-encoded endonucleases [18 bp in one case (21)] could allow targeting of a single specific site in a genome, either by the good fortune of having a usable site already in the genome or by the one-time introduction of a "landing site" containing the endonuclease recognition site and flanking exon homology to some shuttle vector construct.

A9259.

Pasteur's argument that this is "mere speculation" rather than a suggestion or motivation to combine the references is convenient but unfounded. Precision suggests that Eddy92 simply used the circumspect language of scientific publications rather than the all-too-certain language of patent applications and legal briefs.

But there is more in *Eddy92*, including an acknowledgement that the experiments are specifically intended to "mirror" those of *Bell-Pederson* and to determine whether they can be applied in other settings:

> We have configured the experimental system to closely mirror that used to measure the mobility of the mobile [GIIEE] introns. Bell-Pedersen et al. (19) have shown that the [GIIEE] can catalyze the mobility of a foreign gene (for kanamycin resistance or lacZ) within the [GIIEE] exon context as efficiently as the [GIIEE] intron itself.

A9259.

And the Abstract of *Eddy92* concludes with:

> The generality of the mobility mechanism may enable high efficiency targeted gene replacements or disruptions in a variety of organisms.

A9256.

The Board, taking into consideration the entire record, made the factual finding that *Eddy92* provided the requisite motivation to combine the references. "The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact." *In re Gartside*, 203 F.3d at 1316.

Precision submits that the plain language of *Eddy92*, as well as the explicit acknowledgement of copying the experimental design of *Bell-Pedersen*, provides substantial evidence of motivation to combine those references and practice the method in a "variety of other organisms."

C. The Board Correctly Found a Reasonable Expectation of Success to Use the Methods of *Quirk* and *Bell-Pedersen* to Insert Genes into Chromosomal DNA

1. The Board Did Not Err in Finding *Frey* and *Dujon90* Provide a Reasonable Expectation of Success

As noted above, Pasteur's argument that the *Frey* and *Dujon90* references were misinterpreted (Appellant's Br. 41) is a new argument raised on appeal and should not be entertained.

In any event, however, the argument is not only without merit, but is irrelevant in view of Pasteur's own admissions.

For example, Pasteur states that:

> The experiments described in *Frey* were not carried out in yeast cells. They were conducted *in vitro* using chromosomes that were extracted from yeast cells. A9345; A13468-69. Because the experiments were conducted outside of a living cell, the cleavage did not take place "in yeast cells."

Appellant's Br. 41; emphasis in original.

Thus, Pasteur admits that *Frey* shows that GIIEEs are capable of cleaving yeast chromosomal DNA.

Next, Pasteur states that:

> *Dujon90* is a short abstract that described "an artificially placed site within the nucleus"… *Dujon90* was referring to a GIIE endonuclease site located in a plasmid inserted into the yeast nucleus….Thus, when [the GIIEE] was provided to the cell, it cleaved the [GIIEE] recognition site in the plasmid."

Appellant's Br. 42; emphasis in original.

Thus, Pasteur admits that *Dujon90* shows that GIIEEs are capable of cleaving DNA in the nucleus.

It is difficult to see, therefore, how *Frey* and *Dujon90* do not provide substantial evidence that a GIIEE would have a reasonable likelihood of success in cleaving chromosomal DNA in a nucleus when Pasteur admits that it had been shown that (a) a GIIEE can cleave chromosomal DNA and (b) a GIIEE can cleave DNA in a nucleus. Clearly, however, Pasteur has not met its burden of showing the Board acted without substantial evidence.

2. The Board Properly Considered the Potential Toxicity of GIIEEs

As noted above, Pasteur argues that the Board wrongly concluded that the claims "do not expressly require that cells *remain* viable" (emphasis added), and that "viability is an *inherent* requirement in the claims" (emphasis added), and therefore discounted the teachings regarding toxicity in the prior art. Appellant's Br. 43-44. This is a new argument raised on appeal and should not be entertained. In particular, Pasteur is attempting to introduce a new claim interpretation on appeal. This should not be permitted. *In re Watts*, 354 F.3d 1362, 1368 (Fed. Cir. 2004) (parties are often barred from changing the scope of their claim construction position on appeal).

In any event, the issue of toxicity was considered by the Board and is explicitly addressed in a section entitled "Toxicity." A132. The Board considered

the substantial evidence provided in *Quirk*, discussed above in connection with the relevant teachings of the Bell-Pedersen Declaration (A13298-13300), and the teachings of *Frey* and *Dujon90*. Moreover, the Board expressly declined to "import limitations from the patent specification into the claims."

Finally, with respect to the merits of Pasteur's argument, it is apparent from the cited prior art that toxicity was known and that steps were taken to mitigate it (*e.g.*, *Quirk*, paragraph bridging pgs. 456-457, A12536-12537), but that those of skill in the art nonetheless considered the toxicity acceptable (at least for some applications) and therefore suggested the use of the claimed methods "in a variety of organisms" (*e.g.*, *Eddy92*, pg. 1547, last paragraph, A9259). Therefore, the art considered by the Board clearly provided substantial evidence to support the Board's conclusion.

D. The Board Correctly Considered Pasteur's Objective Evidence of Nonobviousness

Pasteur's arguments regarding secondary considerations of non-obviousness were carefully considered by the Board and consumed at most six pages of the Board's decision. A133-138. Simply put, Pasteur's evidence failed to show a nexus between the *claimed* invention and any of the objective evidence of non-obviousness. Therefore, the Board's factual finding should not be disturbed.

II. THE OBVIOUSNESS REJECTION FOR CLAIM 14 OF THE '605 PATENT SHOULD BE AFFIRMED

Claim 14 of the '605 Patent covers a method for inserting a gene of interest into a specific site in the chromosomal DNA of an organism by using a GIIEE to promote homologous recombination. A401(70:26-38). The Board found that claim 14 would have been obvious because (1) one skilled in the art would have been motivated to combine *Eddy92* with *Quirk* or *Bell-Pedersen* to perform the claimed invention, A107; and (2) *Frey* and *Dujon90* "mooted" any unpredictability, A108. Both findings were supported by substantial evidence.

A. The Board Correctly Found Motivation to Combine Eddy92 with Quirk and Bell-Pedersen to Perform the Claimed Method

Pasteur's arguments with respect to the non-obviousness of claim 14 of the '605 Patent in view of the combination of Quirk and Bell-Pedersen with Eddy92 are essentially identical as those made for claims 10 and 12 of the '545 Patent. Accordingly, Precision's responses are the same and are not repeated here.

B. The Board Correctly Concluded that Frey and Dujon90 "Mooted" Unpredictability

Pasteur's arguments with respect to the teachings of *Frey* and *Dujon90* in relation to claim 14 of the '605 Patent are essentially identical to those made for claims 10 and 12 of the '545 Patent. Accordingly, Precision's responses are the same and are not repeated here.

C. The Board Correctly Considered Pasteur's Objective Evidence of Nonobviousness

The Board considered Pasteur's "objective evidence of nonobviousness" which was submitted for all three of the Appealed Patents and correctly found that it failed to establish a nexus with the claimed invention, as discussed above in connection with the '545 Patent.

D. Pasteur's Appeal Is Moot Because the Scope of Claim 14 Was Substantially Amended During the Reexamination

Pasteur's argument that the amendment to claim 1, upon which claim 14 depends, adding the term "viable," does not affect the scope of the claim because it was "inherently" present before the amendment, should be rejected. On the contrary, the introduction of the term "viable" into the claims was a substantive amendment intended to overcome a prior art rejection. Pasteur cannot be allowed during reexamination to assert that an amendment overcomes a prior art rejection, and then assert on appeal that the amendment is not substantial.

Specifically, in a Non-Final Office Action dated September 17, 2009, claim 1 was rejected as obvious over *Schiestl* in view of *Frey* (Office Action at 14-15; A3820-3821). After amending claim 1 to add the word "viable," Pasteur argued:

> Moreover, cleavage of chromosomal DNA by a Group I intron encoded endonuclease in an isolated, viable cell could not have been predicted from the teachings of Schiestl and Frey. Prior to Dujon's invention, it was unclear whether or not Group I intron encoded endonucleases would be toxic or lethal to cells . . . Since Schiestl teaches that restriction enzymes introduce aberrant breaks in animal

> chromosomes, not targeted breaks, and that these aberrant breaks result in chromosomal abnormalities and reduced viability, and Frey does not use I-SceI, or any other endonuclease in the context of a cellular environment, it would be impossible to predict whether or not I-SceI would induce targeted cleavage of an endonuclease recognition site at a location in the chromosomal DNA of a viable cell as is presently claimed.

(Patent Owner's Response dated November 17, 2009, at 39, A4066).

Thus, the amendment adding the term "viable" was clearly intended as a substantial amendment to distinguish between the cells of the claimed invention and the cells of the prior art *Schiestl* reference.

Furthermore, Pasteur's arguments are once again internally inconsistent. On the one hand, Pasteur argues that the invention was non-obvious over references such as *Quirk* or *Bell-Pedersen* because the toxicity of GIIEs made it unclear that the invention could work, while arguing on the other hand that cells in which homologous recombination is shown to occur, which would include the cells of *Quirk* and *Bell-Pedersen*, are inherently viable because the "homologous recombination requires a function cell." Appellant's Br. 52.

III. THE OBVIOUSNESS REJECTION FOR THE CLAIMS OF THE '252 PATENT SHOULD BE AFFIRMED

The claims of the '252 patent cover a recombinant mammalian chromosome containing an exogenous GIIE endonuclease site. The Board found that the claims would have been obvious because (1) one skilled in the art would have been motivated to combine either *Old* or *Eddy92* with *Quirk* and *Bell-Pedersen* to make

the claimed invention, and (2) there was no evidence that it would have been unpredictable to make a recombinant mammalian chromosome having an exogenous GIIEE recognition site. Neither finding was supported by substantial evidence.

A. Pasteur Should Not Be Permitted to Raise New Arguments on Appeal

"The Board is an expert body that plays an important role in reviewing the rejection of patent applications. In a proceeding before the Board the applicant is given full 'opportunity to bring forth the facts thought necessary to support his or her position.'" *In re Watts*, 354 F.3d 1362, 1367 (Fed. Cir. 2004) (quoting *In re Gartside*, 203 F.3d 1305, 1314 (Fed. Cir. 2000). The Federal Circuit's "review of the Board's decision is confined to the 'four corners' of [the] record." *Id.* Therefore, "it is important that the applicant challenging a decision not be permitted to raise arguments on appeal that were not presented to the Board." *Id.*

Failure of an appellant to raise an issue before the Board therefore waives the argument on appeal absent special circumstances. *See In re Suitco Surface, Inc.*, 603 F.3d 1255, 1261 (Fed. Cir. 2010) ("Without any reason for its decision not to separately argue claim 6 before the Board, Suitco has waived its separate anticipation argument on appeal."); *In re Watts*, 354 F.3d at 1368 ("Because the appellant failed to argue his current interpretation of the prior art below, we do not have the benefit of the Board's informed judgment on this issue for our review.

Moreover, Watts has shown no reason why we should excuse his failure to raise this argument before the Board."). The Federal Circuit's rule with respect to arguments waived before the Board "is the same rule we follow in appeals from district courts and other agencies." *In re Watts*, 354 F.3d at 1368.

"While appellate courts are given the discretion to decide when to deviate from this general rule of waiver, we have explained that 'prudential considerations' articulated by the Supreme Court counsel against hearing new arguments for the first time on appeal absent limited circumstances …" *Golden Bridge Tech., Inc. v. Nokia, Inc.*, 527 F.3d 1318, 1322-1323 (Fed. Cir. 2008) (citing *Singleton v. Wulff*, 428 U.S. 106, 121 (1976)).

"[T]o prevent a party from clarifying or defending the *original scope* of its claim construction, or from supporting its *existing claim construction* position with new citations to the specification,' we have often barred parties from changing the scope of their claim construction position on appeal." *In re Watts*, 354 F.3d at 1368 n.3 (quoting *Interactive Gift Express, Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1346 (Fed. Cir. 2001)).

As discussed below, Pasteur's assertion that the term "endonuclease site" "requires more than a DNA sequence encoding a GIIEE cleavage site" but, rather, "requires a functional site – *i.e.*, a site that *will recognize* a GIIEE endonuclease

and will be cleaved by a GIIEE endonuclease" (emphasis added) is a new argument and a new claim construction introduced on appeal. Appellant's Br. 61.

B. The Board Correctly Found that Old and Eddy92 Provided Motivation to Engineer a Mammalian Chromosome For Use In The Methods Of Quirk And Bell-Pedersen

1. The Board Correctly Found that *Old* Provided Motivation to Insert the GIIE Endonuclease Site of *Quirk* and *Bell-Pedersen* into a Mammalian Chromosome

The Board relied upon one very clear quotation from *Old* for its finding of fact (A67) that *Old* provided motivation to use the method of *Bell-Pedersen* in mammalian cells:

> The armoury of techniques available to the gene manipulator allows any cloned gene sequence to be altered as desired *in vitro*. It would be a great advance if such alterations could be engineered into copies of a chosen gene within the chromosomes of a living animal cell. The strategy for achieving this desirable aim is to bring about the change in the endogenous gene through homologous recombination between it and incoming mutated copies of the gene introduced by a DNA transfection procedure. If this capability were available for mouse cells it would, for example, be possible to introduce a mutation into a chosen gene within embryo-derived stem (ES) cells in culture. These cells can then be incorporated into mouse embryos at the blastocyst stage.

A10075.

From this, the Board correctly concluded that there was motivation in the art to use mammalian cells in methods of homologous recombination and, as *Quirk* and *Bell-Pedersen* disclosed a new method of promoting homologous recombination, it would have been obvious to introduce a GIIEE recognition site in

a mammalian chromosome. "The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact." *In re Gartside*, 203 F.3d at 1316.

Precision submits that the plain language of *Old* provides substantial evidence of motivation to combine those references and produce the claimed mammalian chromosomes with exogenous GIIEE recognition sites.

2. The Board Did Not Err in Finding that *Eddy92* Provided Motivation to Insert the GIIE Endonuclease Site of *Quirk* and *Bell-Pedersen* into a Mammalian Chromosome

The Board relied upon *Eddy92*, which "specifically mentioned the GIIEE endonuclease system described in Bell-Pedersen," for its finding of fact (A68) that *Eddy92* provided motivation to use the method of *Bell-Pedersen* in mammalian cells. The relevant quotation from *Eddy92*, discussed previously, follows:

> It should be possible to use DSBR-based targeting of homologous recombination to effect site-directed gene conversions in a variety of organisms. The extreme specificity of intron-encoded endonucleases [18 bp in one case (21)] could allow targeting of a single specific site in a genome, either by the good fortune of having a usable site already in the genome or by the one-time introduction of a "landing site" containing the endonuclease recognition site and flanking exon homology to some shuttle vector construct.

A9259.

Eddy92 even suggests "the one-time introduction of a 'landing site' containing the endonuclease recognition site" into the target chromosome. *Id*.

Thus, *Eddy92* even more clearly suggests introduction of an exogenous GIIEE site (the 'landing site') into a mammalian chromosome.

From this, the Board correctly concluded that there was motivation in the art to introduce GIIEE sites into the chromosomes of a variety of organisms, including mammals, for use in the methods of homologous recombination of *Quirk* and *Bell-Pedersen*. "The presence or absence of a motivation to combine references in an obviousness determination is a pure question of fact." *In re Gartside*, 203 F.3d at 1316.

Precision submits that the plain language of *Eddy92* provides substantial evidence of motivation to combine those references and produce the claimed mammalian chromosomes with exogenous GIIEE recognition sites.

C. The Board Correctly Found the Claims Obvious

1. The Board Properly Construed the Claims

As noted above, Pasteur argues that the Board wrongly construed the claim term "exogenous Group I intropn encoded endonuclease site," and therefore discounted the unpredictability of the claimed invention, and improperly found it obvious. Appellant's Br. 61-62. This is a new argument raised on appeal and should not be entertained. In particular, Pasteur is attempting to introduce a new claim interpretation on appeal. This should not be permitted. *In re Watts*, 354

F.3d 1362, 1368 (Fed. Cir. 2004) (parties are often barred from changing the scope of their claim construction position on appeal).

In any event, the Board did in fact properly construe the term as referring to "a DNA sequence which is *recognized by* the GIIEE endonuclease" (A60), rather than "a site that *will recognize* a GIIEE endonuclease". Appellants's Br. at 61 (emphasis added). Rather than showing error in the Board's claim construction, Precision submits that it is Pasteur that has proffered an erroneous construction.

2. Pasteur Did Not Provide Evidence Showing Unpredictability in Making a Recombinant Mammalian Chromosome with an Exogenous GIIEE Site

Pasteur provides arguments relating to various reasons that a GIIEE site in a mammalian chromosome may be cleaved *in vivo* in a mammal, but the claim does not require cleavage *in vivo*, and the arguments are completely irrelevant to whether one could make and use such a chromosome for other applications, such as the genome mapping described in the specification ("This invention also relates to the use of I-SceI for mapping eukaryotic genomes and for in vivo site directed genetic recombination", col. 1, ll. 23-25, A283).

Therefore, Precison submits that Pasteur's arguments are irrelevant and do not raise a true issue for appeal.

D. The Board Correctly Considered Pasteur's Objective Evidence of Nonobviousness

Pasteur's arguments regarding secondary considerations of non-obviousness were carefully considered by the Board and discussed in the Board's decision. A71. Simply put, Pasteur's evidence failed to show a nexus between the *claimed* invention and any of the objective evidence of non-obviousness. Therefore, the Board's factual finding should not be disturbed.

CONCLUSION

For the foregoing reasons, the Board's obviousness decisions should be affirmed as to claims 10 and 12 in the '545 Patent, claim 14 in the '605 Patent, and all claims in the '252 patent.

Respectfully submitted.

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CERTIFICATE OF SERVICE

I hereby certify that on this 18th day of April, 2013, I filed the foregoing Brief for Appellee Precision Biosciences, Inc. with the Clerk of the Court via the CM/ECF system, which caused a copy to be served on the following registered CM/ECF users:

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CERTIFICATE OF COMPLIANCE

Pursuant to Federal Rule of Appellate Procedure 32(a)(7)(C), the undersigned hereby certifies that this brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B)(i).

1. Exclusive of the exempted portions of the brief, as provided in Federal Rule of Appellate Procedure 32(a)(7)(B), the brief contains 7,980 words.

2. The brief has been prepared in proportionally spaced typeface using Microsoft Word 2000 in 14 point Times New Roman font. As permitted by Federal Rule of Appellate Procedure 32(a)(7)(B), the undersigned has relied upon the word count feature of this word processing system in preparing this certificate.

/s/ Michael J. Twomey
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